REMARKS

Applicant's attorneys ("Applicants") appreciate the Examiner's review of the Response filed December 19, 2008. Applicants have carefully reviewed the application in light of the Final Office Action mailed March 25, 2009 by the U.S. Patent and Trademark Office ("the Office"). The following remarks are respectfully submitted to illustrate that the application is in condition for allowance.

By this response, Claims 1 and 2 are amended and claim 12 is cancelled. No new matter has been added by this Amendment. Support for the claim amendments can be found in at least the claims and the specification, including, for example, at [0017], [0093] of the published application, and original Claim 1. As such, Claims 1-5, 7-11 and 13-27 are pending in the application and submitted for reconsideration.

REJECTIONS UNDER 35 U.S.C. § 112, 1ST AND 2ND PARAGRAPH

The Examiner has rejected Claim 2 under 35 U.S.C. § 112, ¶1 as allegedly citing compounds not supported by the specification, specifically stearic acid and oleic acid as being surfactants or lubricants. Office Action at page 2. Applicants respectfully disagree. The specification clearly supports that the at least one surfactant and/or lubricant can be anionic surfactants and "stearic and/or oleic acid" may be preferred. *See*, specification publication at [0017]; *see also* [0093], [0142]. As such, Applicants respectfully request this rejection be withdrawn.

Claim 2 is also rejected under 35 U.S.C. § 112, ¶2 as allegedly being indefinite for two reasons. First, Claim 2 states "stearate" then recites "preferably calcium, magnesium, aluminum, or zinc stearate." Applicants have amended this claim to clarify the invention and remove the "preferably" language. Second, Claim 2 recites "an alkaline metal earth metal salt of a fatty acid." Applicants have also amended this claim to clarify this element of the claim. As such, Applicants respectfully request this rejection be withdrawn.

REJECTIONS UNDER 35 U.S.C. § 103(A)

The Office Action has rejected (a) Claims 1–5, 7–12, 17–19, and 21-27 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 4,902,513 ("Carvais") in

view of U.S. Patent No. 6,022,562 ("Autant"); (b) Claim 1-2 and 13-16 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Carvais in view of Autant, and further in view of U.S. Patent No. 6,184,220 ("Turck"); and (c) Claims 1 and 20 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Carvais in view of Autant, and further in view of U.S. PGPub No. 2002/0197327 ("Ulrich").

The burden is on the Examiner to make a *prima facie* case of obviousness, which requires an objective analysis as set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966). In *KSR International v. Teleflex Inc.*, 127 S.Ct 1727, 82 USPQ2d 1385 (2007), the Court affirmed that this analysis includes the following factual inquiries: (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the level of ordinary skill in the pertinent art. Applicants believe an analysis of these Graham factors clearly shows how the instant claims are novel and non-obvious over the prior art.

I. Graham Factors

Scope and content of the prior art

Carvais teaches an oral sustained release medicament containing microcapsules of a drug in a suspension. *See, e.g.*, Carvais at Title, Abstract. The drugs may be water soluble or water insoluble. *See, Id.* at Col. 1, ll. 16-25. The examples teach a water vehicle that is saturated with drug and has microcapsules containing the drug. *See, Id.* at col. 1, ll. 46-49. Applicants concur with the Examiner that the "only detail provided by Carvais about the microparticles in the taught suspension is the presence of drug." Office Action at page 9; *see also*, page 7. The Examiner concludes that "thus these particles must be coated, uncoated, or a collection of both coated and uncoated particles." *Id.* at page 9. Nowhere does Carvais teach a coating composition ensuring that the release profile is not modified after 10 days in an aqueous liquid phase.

Autant teaches microcapsules that consist of particles that are coated with a mixture of at least one film-forming polymer present in the amount of 50 to 90% by dry weight based on the total weight of the coating composition, at least one nitrogen-containing polymer (P2) present in an amount of 2 to 25% by dry weight based on the total weight of the coating composition, at least one plasticizer present in an amount of 2 to 20% by dry weight based on the total weight of

the coating composition, and at least one surfactant or lubricant present in an amount of 2 to 20% by dry weight based on the total weight of the coating composition. *See*, Autant at Col. 6, ll. 55 – Col. 7, ll. 32. The particles are between 50 and 1000 microns. *See, Id.* at Col. 7, ll. 33-35).

Turck teaches oral suspensions of pharmaceutical substances that contain small amounts of highly dispersed silicon dioxide and hydrophilic polymers to form a three-dimensional siloid structure. *See*, Turck at Title, Abstract. The silicon dioxide and hydrophilic polymers allow the suspension to remain homogeneous, a problem this invention attempts to solve. *See, Id.* at Col. 2, ll. 36-39; Col. 2, l. 65 – Col. 3, l. 2.

Ulrich teaches a taste masking composition of capsules with a drug core and a coating formed of water-insoluble enteric coating. *See*, Ulrich at Title, Abstract. The dried microcapsules can be reconstituted with a liquid vehicle by the pharmacist prior to dispensing. *See, Id.* at [0034].

Differences between the claimed invention and the prior art

The instant invention is to an oral medicinal formulation comprising a plurality of drug microcapsules with a specific coating, where the microcapsules are stored in an aqueous solution that is saturated with the drug. Independent claim 1 is to:

> A suspension of microcapsules in an aqueous liquid phase that allows modified release of at least one active principle and is intended for oral administration, wherein said suspension comprises a plurality of microcapsules and an aqueous liquid phase,
>
> wherein the aqueous liquid phase is saturated or becomes saturated with active principle(s) on contact with the microcapsules, and
>
> wherein each microcapsule comprises
>
> (a) a core comprising at least one active principle(s), wherein none of the at least one active principle(s) is amoxicillin and
>
> (b) a film coating that: (i) is applied to the core, (ii) controls the modified release of the active principle(s) in gastrointestinal tract fluids, and (iii) comprises:
>
> (1) at least one film-forming polymer (P1) insoluble in gastrointestinal tract fluids, present in an amount of 50 to 90% by dry weight based on the total weight of the coating

composition, and wherein at least one of said at least one film-forming polymer (P1) is a water-insoluble cellulose derivative;

(2) at least one nitrogen-containing polymer (P2) present in an amount of 2 to 25% by dry weight based on the total weight of the coating composition, and wherein at least one of said at least one nitrogen-containing polymer (P2) is selected from the group consisting of: polyacrylamide, poly-N-vinylamide, and poly-N-vinyllactam;

(3) at least one plasticizer present in an amount of 2 to 20% by dry weight based on the total weight of the coating composition, and wherein at least one of said at least one plasticizer is selected from the group consisting of: glycerol esters, phthalates, citrates, sebacates, cetyl alcohol esters, and castor oil; and

(4) at least one surfactant or lubricant present in an amount of 2 to 20% by dry weight based on the total weight of the coating composition, and wherein at least one of said at least one surfactant or lubricant is selected from the group consisting of: anionic surfactants, non-ionic surfactants, and lubricants, and mixtures thereof;

and wherein the *in vitro* release profile on day ten of the suspension of microcapsules in an aqueous liquid phase is similar to the release profile on day zero, as measured using a type II apparatus according to the European Pharmacopoeia 3rd edition, in a phosphate buffer medium of pH 6.8, at a temperature of 37°C

The Examiner alleges that independent claim 1 is obvious over various combinations of Autant, Carvais, Turck and Ulrich. Applicants respectfully disagree for several reasons.

Carvais is distinct from the current invention because Carvais does not teach all of the required limitations of the microparticles. In fact, as stated by the Examiner, the "only detail provided by Carvais about the microparticles in the taught suspension is the presence of drug." Office Action at page 9; *see also*, page 7. Carvais is distinct from the current invention because Carvais does not teach a coating composition such that the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero.

Autant is distinct from the current invention because Autant does not teach placing the coated microcapsules in an aqueous solution. Autant also does not teach storing the microcapsules in a saturated solution. Moreover Autant does not teach how to obtain aqueous suspension of coated microcapsules with release profile stable over at least ten days.

Turck is distinct from the current invention because Turck does not teach the required coating of the microcapsules such that the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero.. Turck also does not teach microparticles suspended in an aqueous solution that is saturated with the drug. Ulrich is distinct from the current invention because Ulrich does not teach the required coating of the microcapsules such that the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero.. Ulrich also does not teach microparticles suspended in an aqueous solution that is saturated with the drug. Ulrich also does not teach storing the microcapsules in a saturated solution

Resolving the level of ordinary skill in the pertinent art

A worker in this field would have a B.S. degree in science and work at least as a technician. The Examiner, however, does not address the level of ordinary skill in the art, much less the individual Graham factors. Without a determination of the level of ordinary skill in the pertinent art it is difficult, if not impossible, for the Examiner to ascertain what one of ordinary skill in the art would understand from the combined teachings of the alleged prior art. The differences between the scope and content of the prior art and the claimed invention are such that one of ordinary skill in the pertinent art would not understand the claimed invention to be obvious in view of the combination set forth by the Examiner.

II. 35 USC § 103 Analysis under KSR

The Examination Guidelines for Determining Obviousness Under 35 U.S.C. § 103 In View of the Supreme Court Decision in *KSR International Co. v. Teleflex Inc.* state that, having undertaken the factual inquiries of *Graham*, a rejection under 35 U.S.C. § 103 may be supported by one or more of the following rationales: (1) combining prior art elements according to known methods to yield predictable results; (2) simple substitution of one known element for another to obtain predictable results; (3) use of a known technique to improve similar devices in the same way; (4) applying a known technique to a known device ready for improvement to yield predictable results; (5) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success; (6) variations that would have been predictable to one of

ordinary skill in the art; and (7) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine the prior art reference teachings to arrive at the claimed invention. 72 Fed. Reg. 57526, at 57529 (October 10, 2007).

It's unclear which of the seven 35 U.S.C. § 103 rationales the Examiner is applying. However, for all of these rationales the Examiner must show predictability in the art and/or a reasonable expectation of success. 72 Fed. Reg. 57526, at 57529 (October 10, 2007). Further, the Examiner must consider objective evidence which rebuts such predictability and reasonable expectation of success. *Id.* Here, the Examiner has not met this burden.

The combined prior art elements would lead one of skill in the art to yield predictable results or have a reasonable expectation of success. Autant does not teach placing the coated microcapsules in solution. Carvais does not teach microparticles coated with a film composition such that the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero. Turck does not teach a coated microcapsule placed in a saturated solution. Ulrich teaches suspension with taste making and not at all sustained release. He uses for the taste masking a coating made of enteric polymer, which is insoluble at acidic pH and soluble at a pH above about 5.5. *See*, Ulrich at [0019]-[0020]. Thus, when the coating is placed in an aqueous environment above pH 5.5, the coating is "readily soluble in the intestine and, thereby provides immediate release of the active agent in the intestine." *Id.* at [0019]. When the dry coated microcapsules are placed in solution, Ulrich teaches use of pH stabilizers such as acidifying agents, which decrease pH, to "maintain the integrity of the enteric taste masked coating and to stabilize the pH after reconstitution." *Id.* at [0040]. The use of acidifying agents to avoid the solubilization of the coating is specific to enteric coating and cannot be applied to other coatings.

The coating polymers of the invention have different properties from Ulrich because the coating of the invention does not contain an enteric polymer.

The Examiner alleges that "Carvais in view of Autant et al. makes obvious an aqueous suspension saturated with drug and containing either coated drug particles or both coated and

uncoated drug particles, where the coating contains the claimed constituents". Office Action at page 11. Applicants respectfully disagree for the following reason.

Two of the claimed coating components are water soluble: the nitrogen-containing polymer (P2) and the claimed surfactants. For instance, the nitrogen-containing polymer polyacrylamide has a solubility in water of 215g/100ml and described by practitioners as being "infinitely soluble in water." *See*, Exhibit A. Further, the nitrogen-containing polymers poly-N-vinyllactam and poly-N-vinylamide are also known to be water soluble. *See, e.g.*, U.S. Patent Nos. 6,203,813 at Col. 1, ll. 28-29 (describing poly(N-vinyl lactams) as "hydrophilic"); 4,828,725 at Col. 1, l. 18 (describing "[w]ater soluble polymers such as poly(N-vinylamides").

The claimed surfactants, anionic surfactants and non-ionic surfactants, are water-soluble in the sense that they form, as surfactants, nanometric micelles in water.

One of skill in the art would logically believe that addition of water soluble components to a microcapsule coating in an aqueous medium would not result in a formulation where the coating structure remains unchanged and therefore where the suspension of microcapsules in an aqueous liquid phase provides similar release profile on day ten compared to the profile on day zero.

For this reason, one of skill in the art would not place the Autant coated microcapsules, which have two water soluble components in the coating, in a saturated aqueous solution and expect the release profile at ten days to be similar to the release profile at day zero as presently claimed. If anything, others in the art have attempted to solve this problem in a manner like Ulrich: use polymers where solubility is based on pH, and control the pH of the solution.

Indeed, the present inventors are credited with finding the unexpected and surprising fact that a microcapsule coating containing two water soluble components can maintain a constant permeability when placed in solution for ten days. Evidence of unexpected results must be weighed against evidence supporting *prima facie* obviousness in making a determination of the obviousness of the claimed invention. *In re May*, 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). "[U]nexpected results are evidence of unobviousness." *In re Gershon*, 372 F.2d 535, 538, 152 USPQ 602, 604 (CCPA 1967);*Ex parte Blanc*, 13 USPQ2d 1383 (Bd. Pat. App. & Inter. 1989).

One of skill in the art would logically understand that a coating containing water soluble polymers would not maintain its permeability constant in solution. Thus, water soluble materials would not be used for coatings stored in aqueous solution, because it would be expected that the coating would partly dissolve or swell and change its permeability over time. In this invention, the purpose of the coating is to assure a modified release of the active principle. *See*, Abstract. As the amended claims require, the coated microcapsules stored in solution have to have a release profile after ten days that is substantially similar to the release profile at day 0. To maintain this modified release after ten days, the coating must still maintain its permeability.

Contrary to this common knowledge, the inventors have shown that inclusion of two water soluble coating components yields a coating that maintains its permeability constant when placed in an aqueous solution for ten days. See Examples 1 and 3. This finding is not obvious in light of the knowledge in the field. In addition, none of the references cited by the Examiner would lead one of skill in the art to believe otherwise.

For these reasons, Applicants assert that the invention as claimed is non-obvious over the references, and request the rejection be withdrawn.

DOUBLE PATENTING REJECTIONS

The Office Action also provisionally rejects various claims for nonstatutory obviousness-type double patenting over various applications by themselves or in view of Carvais. Applicants note that each rejection is provisional by procedure, and also notes that the applications used in the provisional rejections are pending.

The analysis employed in an obviousness-type double patenting rejection parallels the guidelines for analysis of a 35 U.S.C. 103 obviousness determination. *In re Braat*, 937 F.2d 589 (Fed. Cir. 1991); *In re Longi*, 759 F.2d 887 (Fed. Cir. 1985). The determination of obviousness is a legal conclusion based on underlying factual considerations. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966). These factual inquiries include:

1. the scope and content of the prior art;
2. the differences between the prior art and claims at issue;
3. the level of ordinary skill in the pertinent art; and
4. objective evidence of nonobviousness (*i.e.*, secondary considerations).

Graham, 383 U.S. at 17; *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1124 (Fed. Cir. 2000). The "determination of obviousness 'does not require absolute predictability of success . . . . [A]ll that is required is a reasonable expectation of success.'" *Brown & Williamson Tobacco Corp.*, 229 F.3d at 1125 (*quoting, In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)).

In levying an obviousness rejection under 35 U.S.C. § 103, the Examiner has the burden of establishing that the prior art references teach or suggests all the claim limitations. *See* M.P.E.P. §§ 2142, 2143. The Supreme Court has also pointed out the "import[ance of] identify[ing] a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the new invention does." *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1741 (U.S. 2007). Here, the Examiner has not met the burden of demonstrating that the pending claims are obvious.

Nonstatutory obvious-type double patenting rejection over U.S. Ser. No. 10/522,252 in view of Carvais

The Office Action has rejected Claims 1-2, 4-5, 7-10, 15, 17-19 and 24-26 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 16-17 and 19-31 of copending Application No. 10/522,252 ("the '252 application") in view of Carvais.

First, Applicants note the priority date of '252 application is July 26, 2002, three months *after* the priority date of this instant application. For this reason alone, the rejection is in err and should be withdrawn. Even despite the priority date, the claims still would not be obvious over the '252 application in view of Carvais. As noted above, the combination of a coating containing two water soluble components with a saturated solution for long term storage, where the drug modified release is the same after ten days, is unexpected and surprising. One of skill in the art would logically understand that a coating formed of water soluble polymers would not maintain its permeability in solution. The Examiner has not shown how the '252 application runs counter to this knowledge. For this reason, Applicants request the rejection be withdrawn.

Nonstatutory obvious-type double patenting rejection over U.S. Ser. No. 11/707,034 in view of Carvais

Claims 1-3, 5, 7-10, 17, 19 and 24-26 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting over claims 1-9, 11-24, 26, 31, 41-50, 58-76, 89-91, 99-101 and 113 of copending Application No. 11/707,034 ("the '034 application") in view of Carvais. The priority date of the '034 application is June 15, 2005, three years *after* the priority date of this instant application. For this reason alone, the rejection is in err and should be withdrawn.

Requirement for Information under 35 CFR 1.105

The Examiner has requested the Applicants disclose all co-pending applications and related applications, and has listed numerous applications and patents the Examiner believes may raise double patenting issues.

First, the numerous applications listed have a priority date *after* the priority date of the instant application, including U.S. Application Nos. 11/902,741, 11/884,549, 11/884,534, 11/883,935, 11/802,610, 11/791,466, 11/651,577, 11/648,605, 11/449,675, 11/439,247, 10/997,836, 10/996,780 and 10/580,037. Thus a double patenting rejection is improper.

Further, the following application is abandoned, thus a double patenting rejection cannot apply: U.S. Application No. 11/358,047.

The other remaining applications are in no way obvious variants of the instant claims. For instance, U.S. Application No. 11/723,553 claims coated microparticles combined with a continuous external phase of excipients, including polyeletrolytic hydrophilic polymers that gel/crosslink, neutral hydrophilic polymer, and a gelling or crosslinking additive having cation with a valency of two or more; where when placed in solution the mixture forms a solid gel. Further, U.S. Application No. 10/826,690 claims a completely different coating film formed of a hydrophilic polymer A and hydrophilic compound B. These two applications are in no way similar to the coated microparticles and saturated aqueous solution of the instant invention. Thus, the Office cannot sustain be any double patenting.

CONCLUSION

Applicant believes the application is now in condition for allowance. Reconsideration and withdrawal of the rejections are requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned below.

Applicants submit concurrently a request for a three-month extension of time under 37 C.F.R. 1.136 and the accompanying fee. Please charge our Credit Card in the amount of $1,110, covering the fee set forth in 37 CFR 1.136(a). In the event that any additional extension of time is necessary to prevent the abandonment of this patent application, then such extension of time is petitioned. The Director is hereby authorized to charge any deficiency in the fees filed, asserted to be filed or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Deposit Account No. 50-2228, from which the undersigned is authorized to draw, under Order No. 022290.0120PTUS.

Dated: September 25, 2009

Respectfully submitted,

By _____

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